Original Article

Predictors and outcomes of ischemia-driven target lesion revascularization in deferred lesion based on fractional flow reserve: a multi-center retrospective cohort study

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Background: Fractional flow reserve (FFR) has become the gold standard for diagnosing ischemia in angiographically intermediate epicardial coronary artery stenosis. This study investigated the clinical outcomes and predictors of revascularization deferral based on FFR.

Methods: In this retrospective cohort study, we assessed 474 lesions (440 patients) where revascularization was deferred based on the FFR value. Minimum lumen diameter and %-diameter stenosis were measured. Calcification was graded as none, mild, moderate, or heavy. The synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) score I was also determined. The primary outcome was ischemia-driven target lesion revascularization (TLR) in deferred lesions within 3 years. Patients were also assigned into two groups based on FFR value.

Results: The average age of the patients was 69.7±10.4 years. The average FFR value was 0.86±0.05. Stable angina pectoris was noted in 298 (67.7%) cases, and in-stent restenosis (ISR) was present in 28 (5.9%). The average SYNTAX score was 7.2±4.2. The 3-year ischemia-driven TLR was 18 lesions (3.8%). Cox proportional hazard model revealed that the SYNTAX score and ISR were independent predictors for TLR in deferred lesions [hazard ratio (HR) =1.10, 95% confidential interval (CI): 1.01–1.19, P=0.03; HR =6.33; 95% CI: 2.25–17.8, P<0.01, respectively]. The deferral group, with a low FFR value, tended to have higher TLR rates than other groups.

Conclusions: Lesions with lower FFR values were associated with a higher incidence of ischemia-driven TLR than those with higher FFR values. SYNTAX score and ISR were predictors for ischemia-driven TLR at 3 years in the deferred lesions.

Keywords: Fractional flow reserve; SYNTAX score; in-stent restenosis

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Introduction

Fractional flow reserve (FFR) has become the gold standard for the diagnosis of ischemia in angiographically intermediate epicardial coronary artery stenosis lesions and the use of percutaneous coronary intervention (PCI) (1,2). Although FFR, in addition to angiography, has been reported to be a valuable tool in improving long-term outcomes (3-5), adverse clinical events still occur in patients with high FFR (6). In fact, in the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) trial, the rate of major adverse cardiac events (MACE) in the FFR group was 13.2% at 1 year and 20% at 2 years (3,4).

Several papers have described ischemia-driven target lesion revascularization (TLR) in patients with deferral of revascularization based on FFR in the actual clinical setting (7-11).

On the other hand, several studies have also described that overall coronary atherosclerosis may also influence the incidence of MACE, irrespective of the FFR value, in deferral lesions (12,13). The synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) score is a lesion-based scoring system that predicts clinical outcomes after PCI in patients with multivessel coronary artery disease, on the basis of data derived from coronary angiograms alone (14,15). It is reportedly a reliable indicator of overall coronary atherosclerosis, and functional SYNTAX score has been thought to be a more effective index to accurately predict MACE (16). However, there is insufficient data on the impact of SYNTAX score on ischemia-driven TLR in deferral lesions. Therefore, in this retrospective cohort study, we investigated the predictors and clinical outcomes of deferral lesions in patients with angiographically intermediate epicardial coronary artery stenosis for which revascularization was postponed based on the FFR value. We present the following article in accordance with the STROBE reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-773/rc).

Methods

Study population

In this retrospective cohort study, we assessed 440 patients (474 consecutive lesions) who underwent coronary angiography for acute coronary syndrome or stable angina pectoris and FFR for intermediate stenosis at nine centers between 2013 and 2017, and for whom data about the 3-year outcome were available.

All the hospitals have experienced and skilled doctors who have performed coronary artery angiopraphy on at least 1,000 cases per year. In all cases included in this study, revascularization was deferred based on FFR cut-off values of 0.80 or 0.75, as well as patient condition. The decision for deferral of revascularization was made by at least two experienced attending doctors specializing in coronary angiography.

However, we excluded patients with (I) cardiogenic shock, (II) chronic total occlusion lesion, (III) graft lesion, (IV) in-stent restenosis (ISR) with previous PCI history (≥2) (V) limited life expectancy due to comorbidity, (VI) drift more than 0.02, (VII) angiography by only single projection, or (VIII) severe valvular disease. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee of Tachikawa General Hospital (No. 19008). Data collection was approved by the local ethics committee, and written informed consent for analysis of anonymized data was obtained from all patients.

Coronary angiography

According to the respective local institutional guidelines, coronary angiography was performed using a 5-French (Fr) diagnostic or 6-Fr guiding catheter, and heparin was administered intravenously before the coronary angiography was performed. Quantitative coronary angiography was performed with optimal projections. The percentage diameter stenosis, minimum lumen diameter, reference vessel size, and lesion length were measured. In addition, lesions were classified into three types: focal, diffuse, and others. Angiographic focal lesions were defined according to previous reports (17-19). Calcified lesions were defined as fixed radiopaque densities seen in the area of the stenosis. These calcified lesions were graded as follows according to a previous report (20): mild, difficult to detect; moderate, easily identifiable; and heavy, when density was similar to that of the spine. According to coronary angiography, syntax score I was calculated based on previous reports (14,15).

FFR measurement

FFR was measured using a commercially available coronary pressure wire (Pressure Wire Certus, St Jude Medical, St Paul, AK; Prestige, Volcano Ltd, Cordova, CA). After administering intracoronary nitrates, the pressure wire

was advanced into the site distal to the stenosis. According to the respective local institutional guidelines, maximal hyperemia was induced through intravenous infusion of adenosine triphosphate (ATP) (150–180 μg/kg body weight per minute) via the forearm or femoral vein, or through intracoronary injection of either ATP (40–80 μg), papaverine (8–12 mg), or nicorandil (2 mg). The drug was used at the discretion of the attending cardiologist. FFR was calculated as the ratio of the mean distal coronary pressure to the mean aortic pressure during maximum hyperemia.

Definitions

Individual patient data on clinical outcomes at 3 years were collected and analyzed. The primary outcome was ischemia-driven TLR in deferral lesion within 3 years. In addition, clinical outcomes, including cardiovascular death and myocardial infarction, which occurred in any coronary arteries within 3 years, were also assessed. Death was regarded as cardiac death unless other non-cardiac causes could be identified. Myocardial infarction was defined according to new or presumed new significant ST-segment-T wave changes, left bundle branch block, pathological Q waves in the electrocardiogram (ECG), imaging evidence of new viable myocardium loss, or any new regional wall motion abnormality identified as an intracoronary thrombus by angiography and an elevation of high-sensitive troponin T level.

ISR was defined as diameter stenosis ≥50% in the vessel segment within the stent or within 5 mm proximal or distal to the stent (21).

In the present study, analysis of death and myocardial infarction outcomes was performed on a patient level. In contrast, analysis of ischemia-driven TLR was performed on lesion level.

Statistical analysis

All statistical analyses were performed using IBM SPSS version 22 (IBM Japan Corp, Tokyo, Japan). Data are presented as number (percent) or mean ± SD.

The patients were divided into two groups based on a median FFR value of 0.86. Overall, the event-free and survival-free curves from clinical outcomes, including ischemia-driven TLR after FFR measurement and all-cause death, were estimated using the Kaplan-Meier method. Thereafter, the event-free curves from clinical outcomes for ischemia-driven TLR after FFR measurement were evaluated in subsets, such as acute coronary syndrome and stable angina pectoris.

In addition, a receiver operating characteristic (ROC) curve analysis was used to identify the SYNTAX score cut-off value for predicting an ischemia-driven TLR in deferral lesions. Furthermore, univariate cox proportional hazard model was performed. Thereafter, using covariates of $P<0.05$, multivariate cox proportional hazard model was conducted to identify predictors for ischemia-driven TLR. Finally, a sensitivity analysis for each gender was used to assess the validity of the study results. For all analyses, a two-sided P value of <0.05 was considered statistically significant.

Results

Baseline characteristics

Table 1 summarizes the baseline characteristics of the 440 consecutive patients, while *Table 2* summarizes the location characteristics of the lesions and the FFR measurements of the 474 lesions analyzed in this study. The mean follow-up term was 973±213 days.

The average patient age was 69.7±10.4 years. Most of the patients were male (n=306, 69.5%). Left anterior descending coronary artery was the most prevalent culprit artery (273 cases, 57.6%). Relatively more simple lesions (Type A) were included. The average SYNTAX score was 7.2±4.2. There were 28 cases of ISR after drug-eluting stent (DES) implantation (5.9%). The prevalence of ISR was not associated with the amount of prior PCI history. Approximately 70% of patients had stable angina pectoris. Overall, the mean FFR value and median FFR [IQR] were 0.86±0.05 and 0.86 [0.83–0.89], respectively.

Clinical data and predictors for TLR in deferred lesions based on FFR value

As shown in *Table 3*, from a lesion perspective, the 3-year ischemia-driven TLR was 18 lesions (3.8%), which consisted of 18 patients. The median time of TLR was 381 [155–751]. However, on a patient basis, myocardial infarction occurred in 9 patients (2.0%), and there were 11 cases of all-cause death, of which cancer and aspiration pneumonia were the main causes (data not shown). On the contrary, cardiovascular death rate was very low (1 case). Five out of 28 cases of ISR (17.8%) developed the 3-year ischemia-driven TLR.

Table 1 Baseline patient characteristics

Variables	Number of patients (N=440)
Age (years) (mean ± SD)	69.7±10.4
Sex (male), n (%)	306 (69.5)
BMI (kg/m^2) (mean ± SD)	25.1±4.8
Hypertension, n (%)	338 (76.8)
Diabetes, n (%)	159 (36.1)
Dyslipidemia, n (%)	283 (64.3)
Smoking history, n (%)	248 (56.3)
Prior PCI, n (%)	146 (33.1)
Prior CABG, n (%)	8 (1.8)
Family history of ischemic heart disease, n (%)	61 (13.9)
Chronic kidney disease, n (%)	157 (35.7)
Hemodialysis, n (%)	25 (5.7)
Clinical presentation, n (%)	
Stable angina	298 (67.7)
Acute coronary syndrome	76 (17.3)
STEMI	4 (0.9)
NSTEMI	32 (7.3)
Unstable angina	40 (9.1)
Unknown	66 (15.0)

SD, standard deviation; BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACS, acute coronary syndrome; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction.

Table 3 Analysis of major adverse cardiac events

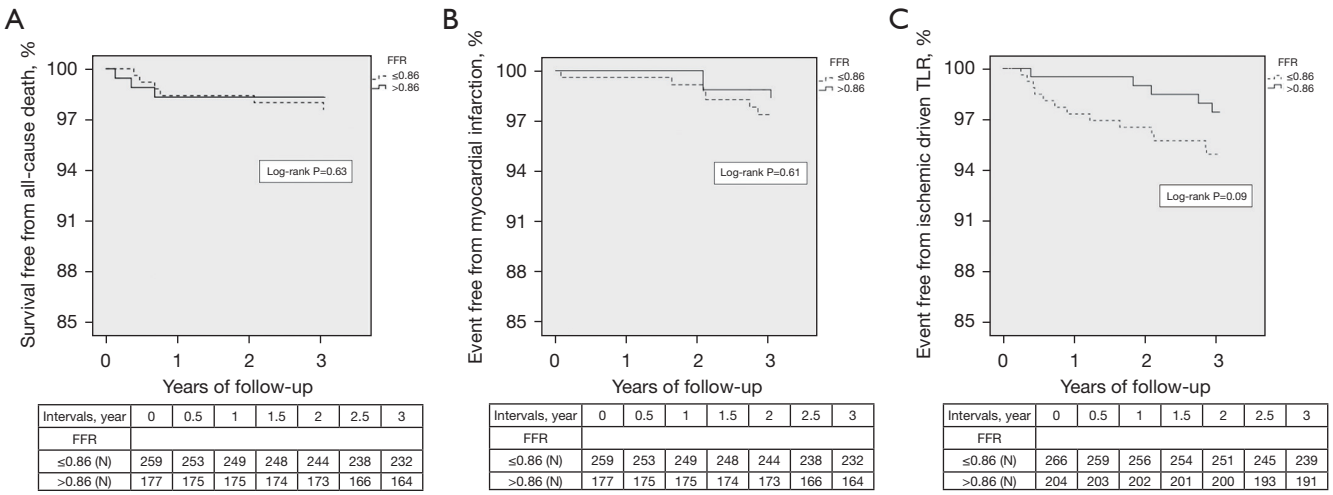
Major adverse cardiac events	Number
Patient level, n (%)	N=440
All-cause mortality	11 (2.5)
Cardiovascular death	1(0.2)
Stroke	7(1.6)
Myocardial infarction	9 (2.0)
Lesion level, n (%)	N=474
Ischemia driven-TLR	18 (3.8)

TLR, target lesion revascularization.

Table 2 Location characteristics of the lesions and FFR measurements

Variables	Number of lesions (N=474)
Location of target lesions, n (%)	
Left main coronary artery	18 (3.8)
Left anterior descending coronary artery	273 (57.6)
Left circumflex coronary artery	86 (18.1)
Right coronary artery	95 (20.0)
ACC/AHA lesion classification, n (%)	
A	226 (47.7)
B1	98 (20.7)
B2	66 (13.9)
C	84 (17.7)
Vessel morphology, n (%)	
Focal (≤10 mm)	307 (64.8)
Diffuse (>20 mm)	66 (13.9)
Other	101 (21.3)
Calcification score, n (%)	
None	77 (16.2)
Mild	307 (64.8)
Moderate	66 (13.9)
Severe	24 (5.1)
In-stent restenosis, n (%)	28 (5.9)
SYNTAX score, mean ± SD	7.2±4.2
Mean FFR, mean ± SD	0.8±0.05
Median FFR [IQR]	0.86 [0.83–0.89]
FFR categories, n (%)	
≤0.8	89 (18.8)
0.81–0.85	161 (34.0)
0.86–0.90	184 (38.8)
0.91–1.0	40 (8.4)
Quantitative coronary analysis result, mean ± SD	
Minimal lumen diameter (mm)	1.5±0.4
Lesion length (mm)	14.0±8.4
Diameter stenosis (%)	50.2±12.7

SD, standard deviation; ACC/AHA, American College of Cardiology/American Heart Association; FFR, fractional flow reserve.

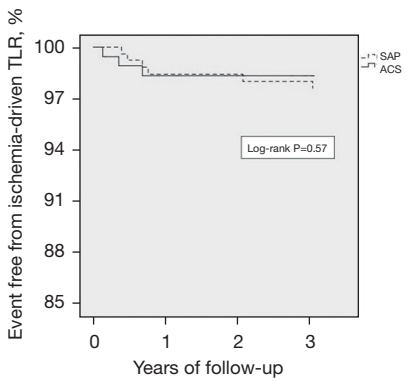


Intervals, year	0	0.5	1	1.5	2	2.5	3
FFR							
≤0.86 (N)	259	253	249	248	244	238	232
>0.86 (N)	177	175	175	174	173	166	164

Intervals, year	0	0.5	1	1.5	2	2.5	3
FFR							
≤0.86 (N)	259	253	249	248	244	238	232
>0.86 (N)	177	175	175	174	173	166	164

Intervals, year	0	0.5	1	1.5	2	2.5	3
FFR							
≤0.86 (N)	266	259	256	254	251	245	239
>0.86 (N)	204	203	202	201	200	193	191

Figure 1 Kaplan-Meier survival curves for freedom from all-cause death (A). Kaplan-Meier curves for freedom from myocardial infarction and ischemia-driven target lesion revascularization during the 3-year follow-up for the two categories of fractional flow reserve; ≤0.86, >0.86 (B,C).



Intervals, year	0	0.5	1	1.5	2	2.5	3
Clinical presentation							
SAP	298	288	281	276	272	270	269
ACS	76	73	72	71	71	71	71

Figure 2 Kaplan-Meier curves for freedom from ischemia-driven target lesion revascularization during the 3-year follow-up according to subsets, such as acute coronary syndrome and stable angina pectoris. See text for details; SAP, stable angina pectoris; ACS, acute coronary syndrome.

Overall, Kaplan-Meier curves for freedom from all-cause death, myocardial infarction (MI), and ischemia-driven TLR during the 3-year follow-up were analyzed according to a median FFR value of 0.86. For ischemia-driven TLR, the deferral group with a low FFR value tended to have higher ischemia-driven TLR than that with a high FFR value (Log-Rank P=0.09) (*Figure 1*).

In addition, though Kaplan-Meier curves for freedom from ischemia-driven TLR were compared in subsets, such as acute coronary syndrome and stable angina pectoris, there was no difference between the two groups (*Figure 2*).

In univariate cox proportional hazard model, syntax score, ISR, minimum lumen diameter, FFR value, and left main coronary artery lesion were identified as covariates of P<0.10, as shown in *Table 4*.

Finally, according to multivariate cox proportional hazard model, SYNTAX score and ISR were independent predictors for TLR in deferral lesions [hazard ratio (HR)=1.10, 95% confidential interval (CI): 1.01–1.19, P=0.03; HR =6.33; 95% CI: 2.25–17.8, P<0.01, respectively] (*Table 4*). Likewise, sensitivity analysis for each gender was used to assess the validity of the study result, which resulted in similar findings (data not provided).

ROC curve analysis showed that the cut-off value of SYNTAX score to predict ischemia-driven TLR in deferral lesions was 11.0 (*Figure 3*).

Discussion

The study shows that SYNTAX score and ISR were associated with TLR in deferral lesions at 3 years. Several reports on the clinical outcomes of patients with revascularization deferral based on FFR in the clinical setting exist; however, the present study is the first to report an association between SYNTAX score and ischemia-driven TLR in deferral lesions.

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Table 4 Predictors of 3-year ischemia-driven TLR

Variables	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Age	0.99	0.95–1.03	0.80			
Sex (female)	1.54	0.50–4.69	0.44			
BMI	1.00	0.90–1.10	0.96			
Family history of ischemic heart disease	0.36	0.05–2.71	0.32			
Smoker	1.59	0.59–4.24	0.35			
Hypertension	0.60	0.22–1.62	0.31			
Diabetes	1.13	0.44–2.93	0.79			
Dyslipidemia	0.84	0.32–2.18	0.73			
Acute coronary syndrome	0.45	0.12–1.57	0.21			
Hemodialysis	2.36	0.54–10.29	0.25			
SYNTAX score	1.08	1.01–1.17	0.04	1.10	1.01–1.19	0.03
Left main	1.80	0.86–3.76	0.09			
LAD	0.98	0.72–1.36	0.94			
LCX	0.89	0.62–1.29	0.56			
RCA	0.89	0.26–3.09	0.86			
FFR value (median value >0.86)	0.40	0.11–1.18	0.09			
Focal lesion >20 mm	0.74	0.26–2.08	0.57			
Moderate to severe calcified lesion	0.66	0.13–3.30	0.61			
In-stent restenosis	6.10	2.17–17.13	<0.01	6.33	2.25–17.8	<0.01
Minimal lumen diameter	0.30	0.08–1.18	0.08			
Calcium score ≥2	0.66	0.19–2.28	0.52			

TLR, target lesion revascularization; HR, hazard ratio; CI, confidence interval; BMI, body mass index; ACC/AHA, American College of Cardiology/American Heart Association; FFR, fractional flow reserve; LAD, left anterior descending coronary artery; LCX, left circumflex artery; RCA, right coronary artery.

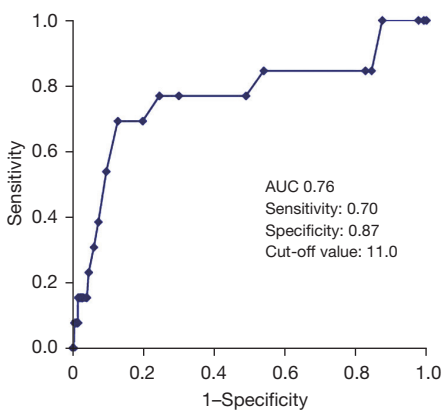

Figure 3 ROC curve analysis for SYNTAX score to predict ischemic-driven TLR in deferral lesions. See text for details. TLR, target lesion revascularization; ROC, receiver operating characteristic curve.

revascularization is to identify lesions in which deferral is likely to be safe (3). Moreover, PCI for coronary stenosis without inducible ischemia (FFR >0.80) may not improve the prognosis (22).

According to recent randomized and observational studies, FFR has been shown to successfully identify lesions that can be safely managed conservatively among angiographically moderate lesions (4,5,9,23,24). The usefulness of FFR has been emphasized in the above-mentioned studies, including those conducted in Japan (7,8).

In the present study, the prevalence of TLR of deferral lesion was approximately 4%, which was comparable to that of previously published trials from Japan (7,8).

In previous reports, from lesion-specific and patient perspectives, lower FFR value, moderately to severely

calcified lesion, minimum lumen diameter, diabetes mellitus, hemodialysis, left main coronary artery lesion, right coronary artery lesion, and acute coronary syndrome have been reported as predictors for TLR of deferral lesion based on FFR (7,8,10,11). In the present study, as shown in *Figure 1*, a lower FFR value was associated with a higher incidence of ischemia-driven TLR in deferral lesions by Kaplan Meyer analysis, which was based on median FFR value, in line with the previous report (7). Although the left main coronary artery and minimum lumen diameter tended to have higher ischemia-driven TLR in the univariate analysis, only minimum lumen diameter tended to be a predictor for ischemia-driven TLR, not left main coronary artery, hemodialysis, or diabetes mellitus in the present study. However, hemodialysis and diabetes mellitus are reportedly associated with coronary events (25-27). Though speculative, these factors did not remain significant probably because the duration of hemodialysis was not considered, and the definition of diabetes mellitus without considering kinds of medications and diabetes control level might have influenced these results. In addition, since only 18 left main coronary artery cases were enrolled, the statistic power may be insufficient to elucidate whether the left main coronary artery could predict TLR. Furthermore, regarding the acute coronary syndrome clinical setting, the reliability of FFR values to the non-culprit artery at an acute phase in a case of ST elevated myocardial infarction remains controversial (28-31). In the present study, though the incidence of ischemia-driven TLR was compared by the breakdown of subsets such as acute coronary syndrome and stable angina pectoris, there was no difference between the two groups. However, ST-elevation myocardial infarction in the acute coronary syndrome group consisted of only 4 cases. Therefore, a definite conclusion was not drawn from the present findings. In addition, the benefit of using FFR to guide PCI in multi-vessel disease in unstable angina and non-ST-elevation myocardial infarction may be different from that in ST-elevation myocardial infarction.

On the other hand, in the present study, SYNTAX score and ISR were identified as novel predictors for TLR after deferral of revascularization based on FFR. SYNTAX score has been reported to predict clinical outcomes after PCI in patients with multi-vessel coronary artery disease (14,15). Furthermore, a previous report has described that the low-FFR (<0.80) group had more severe stenosis and higher SYNTAX scores (median value 14.0) (6). In addition, functional SYNTAX scores have also been effective in predicting better prognosis in patients with multi-vessel coronary artery disease undergoing PCI (16). Thus, these reports may indicate it is crucial to incorporate the anatomical complexity of the coronary artery into a functional evaluation of such, which suggests the present findings are aligned with the reports mentioned above.

In addition, in the 3V (three-vessel) FFR-FRIENDS trial, the low 3V-FFR group showed a higher event rate than the high 3V-FFR group. The low 3 V-FFR was also an independent predictor of MACE (13). Thus, considering these findings and those of the present study, special attention should be given not only to the focal stenotic lesion but also to the overall atherosclerotic conditions, using FFR and SYNTAX score.

In terms of ISR, previous reports have described that FFR measurement in patients with restenosis after bare metal stent implantation and DES seems to be useful in treatment decision making (32,33). Though there is insufficient data describing ISR as an independent predictor of TLR after the deferral based on FFR value, a study reporting the 12-month clinical outcomes of ISR lesions according to FFR showed that deferral lesions (FFR ≥0.80) demonstrated tendency toward lower incidence of MACE in ISR lesions after DES implantation (32). However, the incidence rate was 10% even in an ISR lesion with FFR ≥0.80. This showed a higher incidence rate than that of the TLR rate of approximately 5% in deferred native lesions (7,8,10). In fact, various factors affecting the outcome of ISR have been reported, which includes under-expansion and neointimal hyperplasia including neoatherosclerosis (34-37). Therefore, even in ISR cases with a higher FFR value, the rate of ischemia-driven TLR may be high compared to native lesions, as shown in this study.

Taken together, in the present study, the incidence of TLR in deferral lesions was low at 3.8%, which supports the efficacy of FFR in clinical practice. However, the study indicates that TLR events are more likely to occur in lesions with lower FFR value. In addition, SYNTAX score and ISR were identified as independent predictors for TLR. Therefore, these factors should be considered in patient treatment. In addition, optimal medical therapy should be performed, especially for those with high risk factors.

Limitations

The present study had a relatively small number of patients compared to that of previous studies. Second, the present study included a wide selection of clinical presentation, including ST-elevation myocardial infarction

and stable angina pectoris. It is known that the incidence rate of cardiovascular events can vary based on clinical presentations (10,38), which may have affected our results. Third, coronary plaque has been reported to affect coronary events (39-41). Therefore, in the present study, intracoronary imaging data should have been collected. Fourth, optimal medical therapy is essential to prevent future cardiac events in patients with deferral lesions; however, it could not be determined whether the medical therapy during follow-up was optimal. Fifth, the present study included only deferral patients according to FFR results, which may have introduced selection bias because they differed according to local institutional guidelines. Therefore, the reasons for the deferral should have been clarified. However, in one of the largest studies performed in Japan, the CVIT-DEFER Registry (8), 506 out of 3,857 lesions were enrolled as FFR <0.80, consistent with the present study results. Furthermore, since this is a high-volume multi-center study, a detailed flow diagram for the entry of patients should have been made. Because the present study is a real-world retrospective study, we must acknowledge this as a limitation. However, in the present study, SYNTAX score and ISR were independent predictors for ischemia-driven TLR of deferral patients. Thus, these findings may be useful in the management of such patients.

Finally, further prospective studies involving more patients to investigate the threshold of SYNTAX score and FFR value are warranted.

Conclusions

Lesions with lower FFR were associated with higher incidence of ischemia-driven TLR than those with higher FFR. Moreover, SYNTAX score and ISR were associated with ischemia-driven TLR at 3 years.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-773/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-773/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee of Tachikawa General Hospital (approval ID 19008). Data collection was approved by the local ethics committee, and written informed consent for analysis of anonymized data was obtained from all patients.

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